

Gastric Eosinophilic Granuloma Related to Anisakiasis Resected by Laparoscopic and Endoscopic Cooperative Surgery

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Abstract. *Background:* Anisakiasis-related gastric eosinophilic granuloma is rare. *Case Report:* Herein, we report a patient with anisakiasis-related gastric eosinophilic granuloma who was treated with laparoscopic and endoscopic cooperative surgery (LECS). A 59-year-old woman was presented to our hospital for further examination of a gastric lesion that was initially diagnosed by a local medical doctor. Esophagogastroduodenoscopy showed a submucosal tumor-like lesion in the lower body of the stomach. Endoscopic ultrasonography showed a heterogeneous hypoechoic submucosal mass lesion in the submucosal layer measuring 10 mm, without evidence of deep involvement. Under a clinical diagnosis of gastrointestinal stromal tumor, the patient underwent LECS. Gross appearance of the resected specimen revealed a 1.5×1.0 cm submucosal tumor-like lesion. Microscopic examination revealed necrosed insects consistent with the characteristics of gastric anisakiasis, around which prominent eosinophilic infiltration and granulomas were observed. This prompted a diagnosis of gastric eosinophilic granuloma related to anisakiasis. *Conclusion:* To the best of our knowledge, this is the second case of gastric eosinophilic granuloma related to anisakiasis resected by LECS in the

English medical literature. LECS might be a useful procedure for minimally invasive therapeutic diagnosis.

Gastric eosinophilic granuloma (GEG) is a rare, localized lesion that is pathologically represented by prominent eosinophil cell infiltration into the submucosal layer and muscular layer of the stomach and micro-vessel proliferation (1). Anisakiasis is a human parasitic infection caused by the accidental consumption of nematodes of the genus *Anisakis* that migrate into the human viscera when raw fish is eaten (2). Humans are only infected accidentally, and the clinical symptoms of gastric anisakiasis are classified as acute or chronic (3). Eosinophilic granuloma related to chronic gastric anisakiasis is a rare entity that – in contrast to sudden severe abdominal pain of the acute type – is typically asymptomatic and difficult to diagnose. Furthermore, the *Anisakidae* larvae are absent, making it even more difficult to diagnose.

Laparoscopic and endoscopic cooperative surgery (LECS) is a precise resection technique reported by Hiki *et al.* that combines less invasive surgery with full-thickness tumor resection to avoid creating excessive defects in the gastric wall (4). It has been used to treat submucosal tumor (SMT) including gastrointestinal tumors with a feasible and safe therapeutic strategy (5). Herein, we report a case of GEG in a 59-year-old woman, which was resected by LECS. We also discuss the clinical features of previously reported cases.

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Case Report

A 59-year-old Japanese woman visited her local doctor for a checkup medical examination. Esophagogastroduodenoscopy (EGD) revealed a gastric SMT, and the patient was referred to our hospital. Her family history was unremarkable, and she had a history of tonsillectomy. The physical examination results were also unremarkable. The laboratory findings on admission were as follows: normal red blood cell count

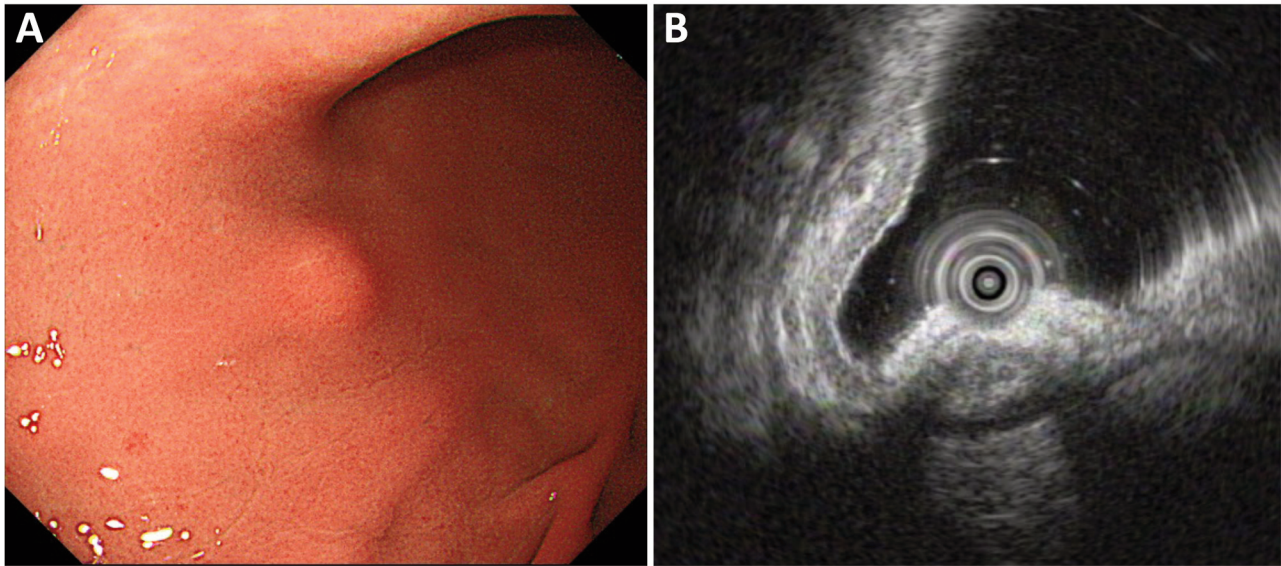


Figure 1. Esophagogastroduodenoscopy and endoscopic ultrasonography reveal a tumor. A submucosal tumor-like lesion is seen on the anterior wall of the lower-third of the stomach (A). Endoscopic ultrasonography shows a heterogeneous hypoechoic submucosal mass measuring 10 mm (B).

($445 \times 10^4/\text{mm}^3$; normal range= $386\text{--}492 \times 10^4/\text{mm}^3$), normal white blood cell count ($4.1 \times 10^3/\text{mm}^3$; normal range= $3.3\text{--}8.6 \times 10^3/\text{mm}^3$), normal eosinophil count ($1.2 \times 10^2/\text{mm}^3$; normal range= $0.2\text{--}3.8 \times 10^2/\text{mm}^3$), and normal C-reactive protein levels (0.03 mg/dl; normal range <0.14 mg/dl). Serum levels of carcinoembryonic antigen (CA) 19-9, CA-125, and CA 72-4 were normal. Electrocardiography, chest radiography, and abdominal plain film radiography results were also normal.

The first EGD, performed one year ago by her local medical doctor, revealed no particular abnormalities in the stomach. The second EGD in our hospital revealed an SMT-like lesion in the anterior wall side of the lower body of the stomach (Figure 1A). Endoscopic ultrasonography (EUS) showed a mass lesion with heterogeneous hypoechogenic appearance in the submucosal layer measuring 10 mm with no evidence of deep infiltration (Figure 1B). Abdominal contrast-enhanced computed tomography (CT) showed no remarkable findings.

Considering a gastrointestinal stromal tumor (GIST) diagnosis, it was decided that the patient should undergo LECS. The tumor location was confirmed first by endoscopic observation to combine the endoscopic and laparoscopic approaches, and subsequent endoscopic submucosal dissection (ESD) was performed to determine an appropriate cutting line without excessive or inadequate margins (Figure 2A). After entire circumferential cutting of the mucosa and submucosal layer using an insulation-tipped diathermic electrosurgical knife, an artificial perforation of the gastric wall from luminal side into the serosal layer along

with the ESD line was created by a needle knife. After that, an ultrasonic coagulation cutting device was inserted into the perforation hole from the serosal side, and a full-thickness incision was carried out under laparoscopy along the cutting line created by ESD (Figure 2B). The hole after resection of the lesion in the stomach was then closed using an intracorporeal running suture.

Gross appearance of the surgically resected specimen revealed a 1.5×1.0 cm SMT-like lesion (Figure 3A). In the cut surface view of the specimen, the mass was well-circumscribed, with a solid whitish lesion (1.5 cm in diameter) within an intact mucosa (Figure 3B). Microscopic examination revealed necrosed insects consistent with the characteristics of gastric anisakiasis in the SMT-like lesion, around which massive eosinophilic infiltration and granulomas consisting of multinucleated giant cells with epithelioid cells were observed (Figure 4A and B). There was no atypical lesion or malignancy in the specimen. Therefore, we diagnosed the patient with gastric eosinophilic granuloma related to anisakiasis.

The postoperative course was favorable, and the patient was discharged 10 days after the operation without any complications, having been in good health with no evidence of the disease for 3 years postoperatively. The patient provided written informed consent for publication of this case report.

Discussion

Herein, we describe an exceptionally rare case of a patient with anisakiasis-related gastric eosinophilic granuloma that

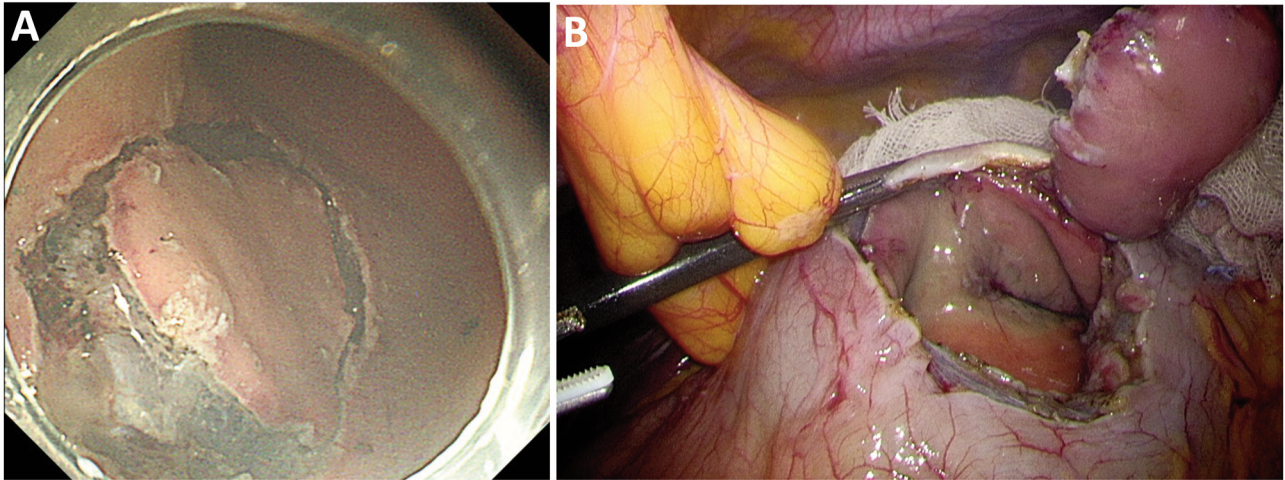


Figure 2. Intraoperative findings during laparoscopic and endoscopic cooperative surgery. A circumferential incision was made around the submucosal tumor-like lesion by an endoscopic submucosal dissection technique using an insulation-tipped diathermic electrosurgical knife (A). The whole layer of the stomach wall was resected along the submucosal incision line using an ultrasonic coagulation cutting device (B).

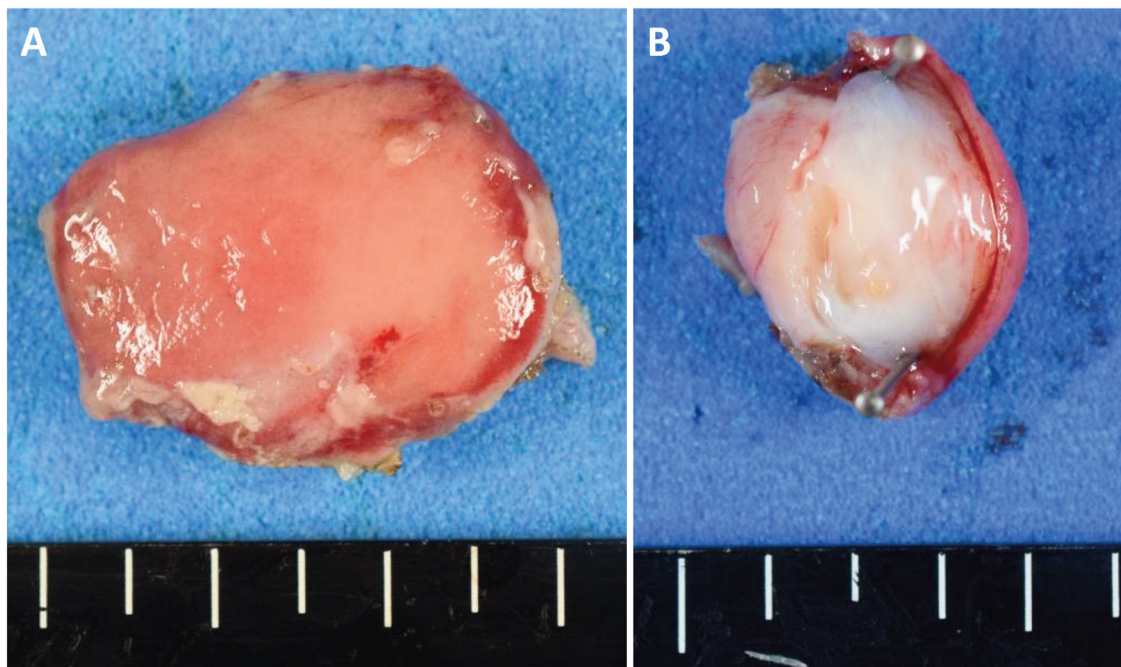


Figure 3. Gross examination of the resected specimen showing a submucosal tumor (SMT) like lesion. Gross appearance of the resected specimen showing an SMT-like lesion on observation from the mucosal side (A). The mass is a well-circumscribed, solid tumor that is 1.5 cm in diameter, visualized within an intact mucosa in the cut surface view (B).

was resected by LECS for therapeutic diagnosis. A Medline and PubMed search for articles in English that were published from 2000 to 2021 was performed using the keywords “eosinophilic granuloma,” “anisakiasis” and

“stomach.” Data concerning patient features and characteristics of the lesions were collected for each patient. To the best of our knowledge, based on the results of this search, the present case is the second report in the English

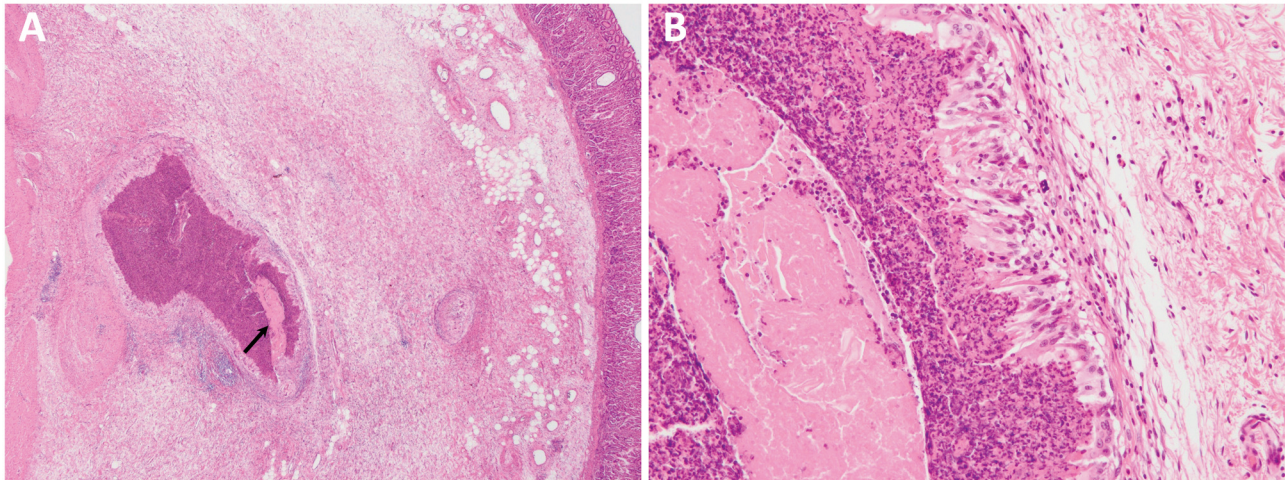


Figure 4. Pathological findings of the surgically resected specimen. A necrosed insect (arrow) and a granulomatous lesion with prominent eosinophilic infiltration in the submucosal tumor-like lesion [(A) magnification, $\times 40$; (B) magnification, $\times 200$].

Table I. Characteristics of the reported cases of anisakiasis-related gastric eosinophilic granuloma.

Author	Year	Age (years)	Gender	Symptom	Gross appearance	Size (mm)	Location	Treatment
Sashiyama <i>et al.</i> (6)	2010	55	Female	Abdominal pain	SMTL	20	M	ESD
Kang <i>et al.</i> (7)	2014	28	Male	Epigastric pain	SMTL with ulcer	30	M	Laparoscopic gastric wedge resection
Kojima <i>et al.</i> (8)	2016	40	Female	Asymptomatic	SMTL	10	M	ESD
Dai <i>et al.</i> (9)	2018	46	Male	Epigastric pain	SMTL with ulcer	60	U	Removal of the larva with biopsy forceps
Tsuji <i>et al.</i> (10)	2020	35	Female	Epigastric pain	SMTL	15	L	LECS
Present case	2021	59	Female	Asymptomatic	SMTL	10	L	LECS

ESD: Endoscopic submucosal dissection; L: lower third of the stomach; LECS: laparoscopic and endoscopic surgery; M: middle third of the stomach; ND: not detected; SMTL: submucosal tumor-like lesion; U: upper third of the stomach.

medical literature of anisakiasis-related gastric eosinophilic granuloma that was resected by LECS.

Table I shows the clinicopathological features of five reported cases (6-10) and the present case. Taken together, the median age was 43 years (range=28-59 years), with a male-to-female ratio of 2:4. Two patients had no symptoms, and gross appearance showed SMT-like lesions in four patients and SMT-like lesions with ulcers in two patients. The median tumor size was 17.5 mm (range=10-60 mm), and asymptomatic lesions accounted for two of the six cases. Gastric lesion was reported in the middle one-third of the stomach in three cases (50.0%), while two patients had a lesion in the lower-third of the stomach (33.3%), and one had a lesion in the upper one-third of the stomach (16.7%). The treatment consisted of LECS in two patients, ESD in

two patients, laparoscopic wedge resection in one patient, and removal of the larva with biopsy forceps in one patient.

Although the cause and pathogenesis of gastric eosinophilic granuloma are still unknown, several considerable mechanisms such as inflammatory reactions, immunologic reactions, and allergic reactions have been reported (1, 10). Li *et al.* reported a significant association in gastric eosinophilic granuloma between mast cells and eosinophil cell count; this suggests that mast cells might be related with eosinophil cells in this disease (1). It has also been reported that most patients with gastric eosinophilic granulomas are young adults, predominantly male (1, 3). However, in our review, there were more female patients than males, and middle-aged patients were the majority of cases with gastric eosinophilic granuloma related to anisakiasis. Furthermore, most patients have ulcers with smooth and

regular edges, but the ulcers in eosinophilic granuloma show clear borders and congested tissues in the adjacent mucosa and submucosal layer (11). However, ulcers were observed only in two cases in our review (7, 9). Considering these differences in characteristics, different pathogenetic factors may operate in gastric eosinophilic granulomas.

Acute anisakiasis infection often causes severe epigastric pain because of the infestation of the gastric wall by larvae. However, diagnosis of chronic anisakiasis infection, which is relatively rare, accounting for 2%-4% of anisakiasis cases (2, 12), is often difficult due to not only non-specific and mild symptoms but also denaturalization and absorption of the larvae in the submucosal layer (6, 13). In some patients, eosinophil counts often increase in the peripheral blood; our patient, however, had normal levels. Park *et al.* reported the typical findings of EUS for chronic gastric anisakiasis were hypoechoic lesions with heterogeneous pattern accompanying hyperechoic tubular structures in the submucosal layer of the stomach (3). For accurate diagnosis, it is exceedingly important to be familiar with this knowledge of EUS findings and pathogenic features presented in this entity.

Nowadays, ESD is widely spread as recommended treatment for curative en-bloc resection of early gastric cancer without risk of lymph node metastasis (6, 14). However, Sashiyama *et al.* reported that ESD was difficult in a case of eosinophilic granuloma treatment due to severe fibrosis; while the SMT-like lesion was completely resected, it was complicated by a tiny perforation, which was managed by the application of endoclips. In the present case, the use of LECS was safe, less invasive, and resulted in the preservation of almost the entire stomach for the consideration of a wide differential diagnosis list for SMT of the stomach. LECS might be one of the appropriate therapeutic strategies for not only the precise resection of gastrointestinal neoplasms, including GIST, but also for obtaining a definitive diagnosis for such cases.

In conclusion, although anisakiasis-related gastric eosinophilic granulomas are rare, physicians should consider this disease as a qualitative differential diagnosis for submucosal tumors. As this disease is difficult to distinguish from malignant disease, LECS is the most feasible option for accurate diagnosis due to its minimally invasive approach. Further assessments resulting from the accumulation of additional cases are required to consolidate the accurate diagnosis and effectiveness of treatments.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this report.

Authors' Contributions

T. Namikawa, A. Marui, K. Yokota, S. Yamaguchi and I. Fukudome performed the surgical procedure; T. Namikawa and H. Maeda

reviewed literature data; T. Namikawa, M. Munekage, S. Uemura and H. Kitagawa performed preoperative investigation the patient; T. Namikawa prepared the draft of the manuscript; M. Kobayashi was advisor of the surgical procedures; T. Namikawa and K. Hanazaki reviewed the final version of the manuscript. All Authors read and approved the final version of the manuscript.

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